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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,867	07/17/2003	Lloyd G. Mitchell	A35306-A 069906.0161	7609

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/621,867	MITCHELL ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 July 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of 9/7/05 has been entered.

Claims 1-59 are pending.

Election/Restrictions

In light of Applicant's response of 9/7/05, all pending claims are rejoined and considered.

Claims 1-59 are considered.

Note, Re: New Subject Matter in CIP

In order to maintain a clear record of the prosecution, the Examiner notes that the new subject matter incorporated into this Application appears to be figures 14-18, and EXAMPLE 8. Essentially, this demonstrates partial correction of Collagen XVII A1 production in GABEB cell line, *in vitro*.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because: Figure 1 contains shading and a legend and the shading and font used makes the contents not legible; and Figures 4, 14B, 14C, 14D, 14E, and 15 are also not clear due to the shading. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Objections

Claim 55 is objected to because of the following informalities: Claim 55 depends from, in the alternative, claims 44, 43 or 44. While the claim itself is clear, the Examiner is lead to wonder if Applicant meant to claim another claim, and hence, the Examiner makes this objection in order to get this discrepancy on the record. Appropriate correction, or explanation, is required.

Specification

Applicant's specification is objected to for not containing a reference to the fact that Application No. 10/198,447 has been abandoned. Also, Applicant's reference to such Application No. is not in a normal format, i.e., it states "10,198,447".

Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11, 13-30, 32-45, and 47-57 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7-23, 25-28, and 30-34 of U.S. Patent No. 6,013,487 to Mitchell, filed 13 December 1996, Patented 11 January 2003. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

At the core of independent Claims 1-3, 16-18, 22-24, 36-38, and 48-50 is the requirement of nucleic acid with one of three structures: (i) at least one target binding domain for a target pre-mRNA, a 3' splice region comprising a branch point and a 3' splice acceptor site, a spacer between the target binding domain and splice region, and a sequence to be trans-spliced to the target pre-mRNA; (ii) at least one target binding domain for a target pre-mRNA, a 3' splice region comprising a 3' splice acceptor site, a spacer between the target binding domain and splice region, and a sequence to be trans-spliced to the target pre-mRNA; and (iii) at least one target binding domain for a target pre-mRNA, a 5' splice site, a spacer between the target binding domain and splice site, and a sequence to be trans-spliced to the target pre-mRNA. Claims 1-3 require this nucleic acid to be within a cell of the skin; Claims 16-18 require this nucleic acid to be encoded in a vector, which vector is comprised within a cell of the skin. Claims 48-50 require the nucleic acid to be within any eukaryotic vector, and Claims 36-38 are simply drawn to the nucleic acid. Claims 22-30 and 31-35, drawn to methods of producing chimeric RNA in such skin cells further require contacting a target pre-mRNA in the cell with the nucleic acid. Dependent claims further limit the claimed nucleic acids to also comprising a 5' donor site (Claims 4, 19, 25, 39, 51), adding a pyrimidine tract to the 3' splice region (Claims 5, 20, 26, 40, 45, 52), safety sequences binding one or more sides of the 5' or 3' splice site

(Claims 6-7, 21, 27, 41, 53), sequences that bind target pre-mRNA by triple helix formation, complimentarity, or protein-nucleic acid interaction (Claims 8, 42), the sequence to be transspliced encoding polypeptides expressed within the cell (Claim 9, 28-30, 43-44, 46), keratinocyte specific or melanoma specific polypeptides (Claims 10, 11, 29-30, 44), melanoma cells (Claim 14, 33), cancer cells (Claim 13, 32-33), keratinocytes, melanocytes, or dermal papilla cells (Claim 15, 35, 44) toxic polypeptides (Claim 34), and Collagen VII or XVII or laminin (Claims 46), and compositions with carriers (Claim 56) which may be applied to the skin (Claim 57) and viral vectors (Claim 54). Independent claims 58-59 encompass methods of correcting genetic defects or imaging gene expression comprising the administration of a nucleic acid with one or more target binding domains for a gene expressed in the skin cell that comprises a genetic defect and a nucleic acid sequence to be trans-spliced, which may be a reporter gene.

Claims 1-5, 7-8, 9-17, 18-23, 25-28, 30, and 32-34 of the Mitchell '487 patent encompass similar nucleic acids, although the independent claims require the safety sequences (Claims 19-20). Moreover, the dependent claims include limitations to further comprising 5' donor sites (Claim 21), the same binding mechanisms (Claims 22, 27), encoding a translatable protein product (Claim 23, 28), toxic polypeptides (Claim 25-26, 30-31). Moreover, such nucleic acids are taught in the specification to be used in transforming cells, and *inter alia*, melanocytes, which are skin cells (col. 16, paragraph 2). Furthermore, Claims 1-5, 7, and 9 are drawn to cells comprising these same nucleic acid molecules; Claims 10-12 are drawn to cells comprising vectors which comprise these nucleic acids; and Claims 13-18 are drawn to similar methods of producing chimeric RNAs in a cell.

Hence, these claims encompass similar subject matter. Moreover, it would have been obvious from Mitchell '487 to make a skin cell comprising these nucleic acids and vectors, as well as to make a chimeric mRNA, correct gene defects, or image gene expression with such nucleic acids in a skin cell. One of skill in the art would have been motivated to do so because Mitchell '487 teaches that melanoma cells are a desired cell type for this treatment/imaging. Moreover, the Artisan would have had a reasonable expectation for success because Mitchell had already shown that such pre-mRNA trans-splicing would occur.

Claims 12, 31, and 46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7-28, and 29-34 of U.S. Patent No. 6,013,487 to Mitchell in view of either Zillikens, et al. (1999) Arch. Dermatol. Res. 291: 187-94 or U.S. Patent No. 5,874,560 to Kawakami, et al., filed 22 April 1994, Patented 23 February 1999.

As reviewed above, Mitchell claims the various aspects having to do with targeting cells with, *inter alia*, a toxin-encoding gene which will target a cell-specific pre-mRNA, and encompasses the same structure as presently claimed. However, what Mitchell does not teach is specific melanocyte gene pre-mRNAs or keratinocyte-specific collagen XVII.

On the other hand, Zillikens teaches that collagen XVII is expressed in keratinocytes (e.g., p. 187, col. 1). And, Kawakami teaches that the angtigen "MART-1" is a protein expressed by melanoma cells (ABSTRACT; col. 2, paragraph 3).

Therefore, the Aritsan would have found it obvious to utilize the nucleic acids, vectors, and cells, and methods of making chimeric RNA with the collagen XVII of Zillikens or the

MART-1 of Kawakami. The Artisan would have been motivated to do so in order to kill these cells *in vitro*. Moreover, the Artisan would have had a reasonable expectation of success, as Mitchell had demonstrated that cells could be killed by such methods, targeting cell-specific pre-mRNAs, and Kawakami had demonstrated that MART-1 was specific keratinocytes.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-15 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The subject matter is directed to skin cells comprising nucleotide sequences that will undergo trans-splicing with endogenously-expressed pre-mRNA sequences. Mansfield, et al. (2004) Trends in Molecular Medicine, 10(6): 263-68 discloses that such trans-splicing mechanisms occur endogenously, albeit rarely, in many species of the animal kingdom (e.g., p. 264, first paragraph). Hence, these claims read on cells untouched by the hand of man. Claims 16-35 are not included in this rejection, because they require the use of vectors and/or introducing such nucleic acids to a skin cell.

It is suggested that Applicant may overcome this rejection by amending the claims to recite that the skin cells are isolated and that the nucleic acid is a heterologous nucleic acid.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 16-18, 22-24, 36-38, 48-50, and 58-59 each recite the limitation "said nucleic acid molecule is recognized by nuclear splicing components". There is insufficient antecedent basis for this limitation in the claim. Specifically, there are two different nucleic acid molecules to which the limitation "said nucleic acid molecule" may apply: the pre-mRNA or the nucleic acid comprising the sequence to be trans-spliced.

Claims 2, 17, 23, 37, and 49 each recite the limitation "the 3' splice region". There is insufficient antecedent basis for this limitation in these claims.

Claims 4-15, 19-21, 25-35, 39-47, and 51-57 are rejected for depending from a rejected base claim and not overcoming the indefinite nature of the base claim.

Claim 6 recites the limitation "the 5' splice site" in Claims 1 or 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 21 recites the limitation "the 3' splice region" in Claim 18. There is insufficient antecedent basis for this limitation in the claim.

Claim 27 recites the limitation "the 3' splice region" in Claim 24. There is insufficient antecedent basis for this limitation in the claim.

Claim 41 recites the limitation "the 3' splice region" in Claim 38. There is insufficient antecedent basis for this limitation in the claim.

Claim 53 recites the limitation "the 3' splice region" in Claim 50. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-59 encompass target binding domains that target any pre-mRNA expressed within any skin cell, any safety sequence, and any skin-cell specific polypeptide/pre-mRNA.

These target binding domains (one or more) that target binding to any pre-mRNA that is expressed within any cell of the skin, cell-specific polypeptides, and safety sequences are broad in scope, being defined generally on the basis of effect. For target binding domains, any molecule, i.e., nucleotide, protein, chemical, etc., that confers specificity of binding is acceptable (pp. 15-16, paragraph 0035) and such binding may be mediated by any mechanism, including triple helix formation, RNA lassos, antibody interactions, etc. (p. 17, paragraph 0036). Also, the cell-type specific polypeptides are defined as any polypeptide that is expressed in any keratinocyte or melanocyte or skin cell (pp. 14-15). Still also, the safety sequences encompass

any sequence(s) that prevent non-specific trans-splicing, by any mechanism (pp. 18-19, paragraphs 40-41).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant discloses no specific safety sequence, a targeting sequence for intron 51 of Collagen 17A, which is mediated by specific Watson-Crick

base pairing (EXAMPLES), and the skin cell specific proteins Collagen 17 and Plectin (EXAMPLES). However, the specification does not provide any disclosure as to what would have been the required structure which would allow for the desired effect of increased specificity of trans-splicing for safety sequences, specific interaction between any pre-mRNA and the nucleic acid to be transpliced, through any form of interaction, and the core structure of any skin-cell specific polypeptide. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristics are the functional characteristics discussed above.

Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera from each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, given great number of possible of embodiments that may meet each of the above-listed genera, Applicant's limited information is not deemed sufficient to reasonably

convey to one skilled in the art that Applicant is in possession of a generic target binding domain that interacts through any method with a generic target pre-mRNA, a generic cell-specific polypeptide, or a generic safety sequence, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

It is noted that the written description requirement is considered a separate and distinct requirement from the enablement requirement. (*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).)

Claim Rejections - 35 USC § 112

Claims 1-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(a) A nucleic acid molecule comprising:

A target binding domain that targets binding of the nucleic acid molecule to a pre-mRNA intron expressed within a cell of the skin via base-to-base complimentarity;

A 3' splice region comprising a branch point, polypyrimidine tract, and a 3' splice acceptor site, located 3' to the target binding domain;

A spacer region that separates the 3' splice region from the target binding domain; and

A nucleotide sequence to be trans-spliced to the target pre-mRNA located 3' to the splice region,

Wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell;

(b) A nucleic acid molecule comprising:

A target binding domain that targets binding of a nucleic acid molecule to a pre-mRNA expressed within a cell of the skin via base-to-base complimentarity;

A 5' splice site located 5' to the target binding domain;

A spacer region that separates the 5' splice site from the target binding domain; and

A nucleotide sequence to be trans-spliced to the target pre-mRNA, located 5' to the 5' splice site,

Wherein the nucleic acid molecule to be trans-spliced is recognized by nuclear splicing components within the cell;

(c) Vectors encoding such nucleic acid molecules;

(d) Isolated cells comprising the nucleic acid molecule or vector; and

(e) Methods of making a chimeric RNA in a cell of the skin *in vitro*,

does not reasonably provide enablement for any *in vivo* or *ex vivo* cells, vectors, or methods, nucleic acid molecules without the aforementioned structures and spatial relationships, any safety sequences or any form of target pre-mRNA binding. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The invention of Claims 1-59 is broad. At the core of independent Claims 1-3, 16-18, and 22-24, is the requirement of nucleic acid with one of three structures: (i) at least one target binding domain for a target pre-mRNA, a 3' splice region comprising a branch point and a 3' splice acceptor site, a spacer between the target binding At the core of independent Claims 1-3,

16-18, 22-24, 36-38, and 48-50 is the requirement of nucleic acid with one of three structures: (i) at least one target binding domain for a target pre-mRNA, a 3' splice region comprising a branch point and a 3' splice acceptor site, a spacer between the target binding domain and splice region, and a sequence to be trans-spliced to the target pre-mRNA; (ii) at least one target binding domain for a target pre-mRNA, a 3' splice region comprising a 3' splice acceptor site, a spacer between the target binding domain and splice region, and a sequence to be trans-spliced to the target pre-mRNA; and (iii) at least one target binding domain for a target pre-mRNA, a 5' splice site, a spacer between the target binding domain and splice site, and a sequence to be trans-spliced to the target pre-mRNA. Claims 1-3 require this nucleic acid to be within a cell of the skin; Claims 16-18 require this nucleic acid to be encoded in a vector, which vector is comprised within a cell of the skin; and Claims 22-24 require this nucleic acid to be used in making chimeric RNA molecules. Claims 48-50 require the nucleic acid to be within any eukaryotic vector, and Claims 369-38 are simply drawn to the nucleic acid. Claims 22-30 and 31-35, drawn to methods of producing chimeric RNA in such skin cells further require contacting a target pre-mRNA in the cell with the nucleic acid. Dependent claims further limit the claimed nucleic acids to also comprising a 5' donor site (Claims 4, 19, 25, 39, 51), adding a pyrimidine tract to the 3' splice region (Claims 5, 20, 26, 40, 45, 52), safety sequences binding one or more sides of the 5' or 3' splice site (Claims 6-7, 21, 27, 41, 53), sequences that bind target pre-mRNA by triple helix formation, complimentarity, or protein-nucleic acid interaction (Claims 8, 42), the sequence to be transspliced encoding polypeptides expressed within the cell (Claim 9, 28-30, 43-44, 46), keratinocyte specific or melanoma specific polypeptides (Claims 10, 11, 29-30, 44), melanoma cells (Claim 14, 33), cancer cells (Claim 13, 32-33), keratinocytes, melanocytes, or dermal

papilla cells (Claim 15, 35, 44) toxic polypeptides (Claim 34), and Collagen VII or XVII or laminin (Claims 46), and compositions with carriers (Claim 56) which may be applied to the skin (Claim 57) and viral vectors (Claim 54). Independent Claims 58-59 encompass methods of correcting genetic defects or imaging gene expression comprising the administration of a nucleic acid with one or more target binding domains for a gene expressed in the skin cell that comprises a genetic defect and a nucleic acid sequence to be trans-spliced, which may be a reporter gene.

These claims are broad for the aspects of *in vivo* and *ex vivo* use, as well as the use of any type of safety sequence and correcting or imaging any genetic defect in any skin cell of any subject. Moreover, Applicant's disclosed use for such cells is for correcting skin defects, treatment of disorders of the skin, and co-extensive diagnostics of the skin (e.g., p. 2, paragraph 1). Hence, the reasons for making such cells, vectors and nucleic acids, as well as making a chimeric mRNA is directed to such therapies and diagnostics. These broad aspects are not enabled by Applicant's specification in view of the art, because the Artisan would have to perform undue experimentation to reasonably predict the working embodiments.

The state of the prior art and nature of the invention is generally not enabling of new inventions in the field. The reasons for such lack of enablement with regard to new inventions is because it is not reasonably predictable that through any specific route of administration that enough cells would be transformed with the nucleic acid or vector, or enough cells would reach the target tissue tissue, and enough of the cells would incorporate and express enough mRNA which would then trans-splice to enough of the target pre-mRNA to produce enough trans-spliced mRNA and enough protein therefrom to have any therapeutic or diagnostic effect.

Specifically, with regard to the aforementioned aspects, the following articles are supplied with respect to gene therapy, because these articles describe the lack of reasonable predictabilities as discussed in the previous paragraph, and because similar articles for pre-mRNA trans-splicing are not of record. It is stressed, however, that there is no reason to believe that pre-mRNA trans-splicing techniques are not subject to the same limitations, i.e., the nucleic acid still has to reach the target tissues, become transformed, and make enough mRNA to target and undergo enough trans-splicing with the target pre-mRNA to produce enough final mRNA and protein therefrom to have an effect, and do so for a long enough period of time.

While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver

genes efficiently and to obtain sustained expression ... The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

Therefore, in reviewing these references, the Artisan would find that it is not reasonably predictable that through any specific route of administration that enough cells would be transformed with the nucleic acid or vector, or enough cells would reach the target tissue tissue, and enough of the cells would incorporate and express enough mRNA which would then trans-

splice to enough of the target pre-mRNA to produce enough trans-spliced mRNA and enough protein therefrom to have any therapeutic or diagnostic effect

Moreover, with regard to pre-mRNA trans-splicing, the same lack of reasonable predictability exist, as well as other difficulties that must be overcome.

Pergolizzi, et al. (2004) C. R. Biologies, 327 : 695-709 provides a recent review with respect to the specific use of pre-mRNA trans-splicing in genetic therapy (TITLE). Pergolizzi reviews the background of such trans-splicing through two mechanisms, ribozyme-mediated trans-splicing (e.g., pp. 698-700) and spliceosome-mediated trans-splicing, which is of interest here (e.g., pp. 700-706).

Of critical importance, Pergolizzi finds, is the interaction of the trans-splicer and target pre-mRNAs, which occurs by virtue of its complementarity which is inverted with respect to the remainder of the trans-splicer to preserve the antiparallel configuration of the hybrid (p. 700, col. 2, paragraph 3). Hence, the only manner through which such targeting sequences recognize the target mRNA is through base-to-base complimentarity, and the Artisan would not be able to reasonably predict that such interactions could occur through triplex formation or nucleic-acid/protein interactions and further that only mRNAs could be used for such targeting sequences (note that the specification says that any molecule could be used, pp. 15-16, paragraph bridging).

Further, Pergolizzi finds, such hybridization domains, for purposes of splicing, are generally required to be considerably more 5' of the intron's branchpoint and polypyrimidine tract, and not impinging at all on these areas (Id.). Hence, the Artisan would not be able to reasonably predict that any particular safety sequence or any targeting sequence would work,

because they may block the splicing of the pre-mRNAs. Moreover, Pergolizzi specifically states that such targeting size and location within the intron of the hybridization domain for efficient trans-splicing is gene-specific, and must be optimized on a case-by-case basis (pp. 700-01, paragraph bridging). Hence, particularly for *ex vivo* and *in vivo* methods, the Artisan would not be able to predict whether any particular nucleic acid would even work due to blocking of the splicing of pre-mRNAs.

Pergolizzi points to a few examples of models of therapy, including an *in vitro* model of the theoretical correction of cystic fibrosis, by producing 12-15% wild-type CFTR (p. 701, col. 1); however, such does little to enable Applicant's invention because the cells are not skin cells, the target pre-mRNAs are different, being of lung cells. Pergolizzi also discusses two models of *in vivo* therapy: correction of factor VIII hemophilia, and correction of CD40L mutation in H1GM1 (pp. 701-02). However, neither model is applicable to Applicant's invention, because they are directed to non-skin cells and do not involve skin-cell pre-mRNAs. Such is the case because, as was discussed previously, trans-splicing is very gene-specific (last paragraph). Moreover, in discussing the H1GM1 therapy, abberant trans-splicing was found, which caused hyperproliferative disease (p. 702, paragraph 2). Hence, the Artisan would not be able to reasonably predict in any particular trans-splicing effort, whether other trans-splicings may occur that would kill the cells transformed before any desired effect might be seen. Such is further emphasized directly by Pergolizzi, where he states:

> A critical question requiring further study for repair of mutant RNAs is the precision and specificity of the repair process. Trans-splicing must be highly specific in order to limit the number of illegitimate and possibly toxic or immunogenic products generated. In one published report, spliceosomal trans-splicing seemed to lack specificity, with the trans-spliced element appearing on

> unintended target RNAs in mammalian cells []. Attempts to modify the trans-splicer to suppress the nonspecific splicing failed to have the desired effect.

(p. 705, last paragraph).

The Artisan would therefore recognize that when designing such nucleic acids to target any particular pre-mRNA, unforeseen consequences may arise due to abberant trans-splicing, which may destroy the cell(s) in which such trans-splicing occurs before any desired effect is seen.

In closing, Pergolizzi recognizes that:

> Significant improvements are also needed in the efficiency of trans-splicing before it can be considered a mature therapeutic [or diagnostic for that matter] modality. Reported efficiencies for spliceosome-mediated pre-mRNA trans-splicing have rarely exceeded ten percent, with most being closer to two percent [], although segmental trans-splicing may be more efficient []. Evidence suggesting nacent transcripts assemble with splicing factors and undergo splicing co-transcriptionally raises some theoretical obstacles to improving the efficiency of trans-splicing []. ... This may impose steric limits to the amount of any trans-splicer that might gain access to the nacent pre-mRNA, and thus to the degree of trans-splicing that occurs [].

(p. 706, second paragraph).

Therefore, while optimistic for the future of such trans-splicing techniques, Pergolizzi recognizes that currently, each method of therapy or diagnostics is specific for that particular gene(s) which are effected, that abberant trans-splicing is not predictable, that unforeseen effects may destroy any cell before the desired effect is observed, that targeting must be by base-pairing, and that safety sequences may block trans-splicing. Moreover, Pergolizzi, in discussing the efficiencies of trans-splicing, points to another area lacking reasonable predictability: segmental trans-splicing (placing to genes to be trans-spliced in the same cell) is much higher than targeting naturally-expressed mRNAs, and rarely do such endogenously-expressed pre-mRNAs undergo trans-splicing more than 2%. Hence, with regard to Applicant's examples and results (discussed

below), such are not reasonably predictable of any particular therapy or diagnostic use or for any cell *in vivo* or used *ex vivo*.

Applicant's specification, broadly discusses pre-mRNA trans-splicing and correction of skin defects (pp. 1-2), epidermolysis bullosa, its genetic bases and therapy efforts (pp. 2-6), structure of the pre-trans-splicing sequences, including that the target sequence may be any nucleotide, protein, chemical compound, etc., safety sequences, spacers, and branch points (pp. 14-19), specific mutations (pp. 19-21), other wide-ranging changes in the exons and introns encoded (pp. 21-23), various other sequences that may be included and assays (pp. 23-24), testing lacZ expression (pp. 24-25), modifications to nucleic acids (pp. 26-30), syunthesis of the trans-splicing molecule (pp. 30-34), and use and administration of such molecules (pp. 34-40). However, such broad description is not the specific guidance and direction that the Artisan would require, given the various aspects of reasonable predictability in the art, i.e., gene delivery to enough cells, expression of enough mRNA and recombination with enough target pre-mRNA to produce enough stable and functioning mRNA and protein therefrom to any effect in any particular disease. Such is further emphasized due to the problems with spliceosome-mediated therapies and diagnostics, i.e., low levels of trans-splicing, abberant trans-splicing, location and structure of the targeting sequences, relative structure of the various sequences with respect to eachother in the sequence comprising the trans-splicing sequence. Moreover, Applicant's discussion of various modifications of such nucleic acids makes it even less reasonably predictable. I.e., would any of these modified nucleic acids, for example, the covalently linked psoralens (paragraph 0062) even transform and transcribe a nucleic acid, or undergo trans-splicing? Furthermore, the forms of binding between the pre-mRNA and the target sequence are

not even known, i.e., triplex formation and protein-nucleic acid interaction, and the safety sequences are likely to degrade the already low-level of trans-splicing that typically occurs as shown by Pergolizzi (above).

Applicant's experiments similarly do not overcome the lack of reasonable predictability in the art. Example 1 demonstrates the reconstitution of the LacZ gene mRNA from two transcribed genes comprising either the 5' or 3' sequence of LacZ and utilizing the collagen 17 intron 51 in various cell lines through trans-splicing *in vitro*. Example 2 demonstrates similar results with a plectin gene intron, and further inclusion of safety domains (which bind the binding point and polypurine tract of the target pre-mRNA) and treatment of individuals, provided in prophetic form. Example 8, newly presented in this CIP, presents a correction of up to 50% of the collagen 17A gene expressed mRNAs in vitro in cells, and presents predictive data concerning correction of collagen 7A. However, while such appears to work, for collagen 17A *in vitro*, the Artisan, due to the reasons above, with regard to pergolizzi would not reasonably predict *ex vivo* or *in vivo* uses to work, which are compounded by the general nature of gene therapy, and further simply showing a single collagen gene, given the rareity in correction seen in Pergolizzi, the Artisan would not even predict any other collagen to be corrected, nor any other gene.

However, Applicant's examples are limited to *in vitro* uses, with reporter genes, and the expression of both pre-mRNAs from plasmids. Pergolizzi has discussed how these results are not predictive of treatment or diagnosis in the case of an engenously expressed pre-mRNA, and such trans-splicing is even less likely to occur (above). Moreover, Applicant's examples do not demonstrate a single functioning safety sequence, any form of triplex formation or protein-

nucleic acid interaction to mediate binding, such trans-splicing always has the structure given in the scope of enablement, in the same relation, and Applicant has not demonstrated any aspect of the enablement would be overcome for any single trans-splicing event such that any treatment or diagnosis, or *in vivo* or *ex vivo* use, or that abberant splicings would not occur, such that these aspects would be reasonably predictable. Moreover, no safety sequences are demonstrated, and the Art does not disclose reasonably predictable safety sequences, and the inclusion of such would likely degrade the already poor level of trans-splicing.

Because of the lack of reasonable predictability, due to the aforementioned difficulties, the Artisan, to reasonably predict the working embodiments, would have to perform undue experimentation to practice the methods, or make the cells *in vitro* or *ex vivo*, to find working safety sequences, to avoid abberant trans-splicing, to find trans-splicing orientations and relations that would work, and to transform enough cells, and produce enough trans-splicing, such that enough cells produce enough spliced mRNA to correct or diagnose anything. Hence, the claims are not enabled for *in vivo*, *ex vivo*, methods of treatment or diagnosis *in vivo* or *ex vivo*, the treatment or diagnosis of any condition, and the sequences not in the orientations or not in the nucleic acids delineated in the scope of enablement above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen, et al. (2000) Mol. Pharmacol., 57(1): 125-34, as evidenced by Mansfield, et al. (2004) Trends in Molec. Med., 10(6): 263-68.

Chen describes melanophores (p. 126, col. 2, paragraph 1). Hence, in view of Mansfield's teaching that these transsplicings occur in nature (p. 264, first paragraph), Chen anticipates Applicant's claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8-11, 14-20, 22-26, 28, 30, 32-40, 42-45, 47-52, 54-55, and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,013,487 to Mitchell, filed 13 December 1996, patented 11 January 2000 and U.S. Patent No. 5,874,560 to Kawakami, et al., filed 22 April 1994, Patented 23 February 1999.

Mitchell teaches the use of nucleic acids for generating chimeric RNA molecules by trans-splicing (ABSTRACT; TITLE). Such nucleic acids are taught to encompass all of the minimal trans-splicing elements of Applicant's claims (e.g., Claims and cols. 4-5). Moreover, Mitchell teaches that such nucleic acids may be used in viral or other vectors, to transform cells (e.g., col. 1, paragraphs 3-4). Furthermore, such nucleic acids may comprise coding sequences for toxins, including diptheria toxin (e.g., col. 3, paragraph 3) to undergo trans-splicing with cell-

specific pre-mRNAs and thereby produce the toxin selectively in those cells producing that pre-mRNA, thereby killing unwanted cells (e.g., col. 6, paragraph 4). Lastly, one such preferred cell type is the melanoma cell (col. 16, paragraph 2). However, Mitchell does not teach a specific pre-mRNA expressed within such cells.

On the other hand, Kawakami teaches that the angtigen "MART-1" is a protein expressed by such meloma cells (ABSTRACT; col. 2, paragraph 3).

At the time of invention by Applicant, it would have been obvious to the Artisan to modify the nucleic acids and vectors and cells of Mitchell, by using melanoma cells, and sequences specific for MART-1 pre-mRNA as taught by Kawakami. The Artisan would have been motivated to do so in order to kill melanoma cells *in vitro*. Moreover, the Artisan would have had a reasonable expectation of success because Mitchell had shown that such pre-mRNA targeting with diptheria toxin would kill cells, and Kawakami had shown the MART-1 to be specific for melanoma cells.

Claim Rejections - 35 USC § 103

Claims 1-5, 8-10, 15-20, 22-26, 28-29, 35-40, 42-44, 47-52, 54-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,013,487 to Mitchell, filed 13 December 1996, patented 11 January 2000 and U.S. Patent No. 6,057,298 to Roop, et al., filed 30 May 1995, Patented 2 May 2000.

Mitchell teaches the use of nucleic acids for generating chimeric RNA molecules by trans-splicing (ABSTRACT; TITLE). Such nucleic acids are taught to encompass all of the minimal trans-splicing elements of Applicant's claims (e.g., Claims and cols. 4-5). Moreover,

Mitchell teaches that such nucleic acids may be used in viral or other vectors, to transform cells (e.g., col. 1, paragraphs 3-4). Furthermore, such nucleic acids may comprise coding sequences for toxins, including diptheria toxin (e.g., col. 3, paragraph 3) to undergo trans-splicing with cell-specific pre-mRNAs and thereby produce the toxin selectively in those cells producing that pre-mRNA, thereby killing unwanted cells (e.g., col. 6, paragraph 4). Lastly, such may produced in any cell type (e.g., col. 1, paragraph 1). However, Mitchell does not teach a specific pre-mRNA expressed within keratinocyte cells.

On the other hand, Roop teaches Keratin K1 (ABSTRACT) and its specificity for keratinocytes (e,g., col. 3, paragraph 5; col. 9, paragraph 2).

At the time of invention by Applicant, it would have been obvious to the Artisan to modify the nucleic acids and vectors and cells of Mitchell, by using keratinocytes, and sequences specific for Keratin K1 pre-mRNA as taught by Roop. The Artisan would have been motivated to do so in order to kill keratinocytes *in vitro*. Moreover, the Artisan would have had a reasonable expectation of success because Mitchell had shown that such pre-mRNA targeting with diptheria toxin would kill cells, and Roop had shown the Keratin K1 to be specific for keratinocyte cells.

Claim Rejections - 35 USC § 103

Claims 1-5, 8-10, 12, 15-20, 22-26, 28-29, 31, 35-40, 42-52, and 54-55 rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,013,487 to Mitchell, filed 13 December 1996, patented 11 January 2000 and Zillikens, et al. (1999) Arch. Dermatol. Res. 291: 187-94.

Mitchell teaches the use of nucleic acids for generating chimeric RNA molecules by trans-splicing (ABSTRACT; TITLE). Such nucleic acids are taught to encompass all of the minimal trans-splicing elements of Applicant's claims (e.g., Claims and cols. 4-5). Moreover, Mitchell teaches that such nucleic acids may be used in viral or other vectors, to transform cells (e.g., col. 1, paragraphs 3-4). Furthermore, such nucleic acids may comprise coding sequences for toxins, including diptheria toxin (e.g., col. 3, paragraph 3) to undergo trans-splicing with cell-specific pre-mRNAs and thereby produce the toxin selectively in those cells producing that pre-mRNA, thereby killing unwanted cells (e.g., col. 6, paragraph 4). Lastly, one such preferred cell type is the melanoma cell (col. 16, paragraph 2). However, Mitchell does not teach targeting collagen XVII pre-mRNA expressed within keratinocytes.

On the other hand, Zillikens teaches that collagen XVII is expressed in keratinocytes (e.g., p. 187, col. 1).

At the time of invention by Applicant, it would have been obvious to the Artisan to modify the nucleic acids and vectors and cells of Mitchell, by using keratinocytes, and sequences specific for collagen XVII pre-mRNA as taught by Zillikens. The Artisan would have been motivated to do so in order to kill keratinocytes *in vitro*. Moreover, the Artisan would have had a reasonable expectation of success because Mitchell had shown that such pre-mRNA targeting

with diptheria toxin would kill cells, and Zillikens had shown the collagen XVII to be specific for keratinocytes.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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